PART VII. CRITIQUE OF CONFERENCE

Chairman: Walsh McDermott

PANEL

Justin M. Andrews
Leighton E. Cluff
John H. Dingle
Thomas Francis, Jr.
Harold N. Glassman
Alexander Langmuir
Norton Nelson
W. Barry Wood, Jr.

CHAIRMAN MCDERMOTT: It is proper that I state the purpose of this particular session as I understand it. We have a panel that is to be involved with something called a "critique."

The panel is in no way to summarize the individual reports that have been presented but simply to be quite eclectic and from their electicism attempt to develop certain points that seem to be especially important.

When the Conference opened, Dr. Langmuir presented a concept of airborne infection, and he made it clear that by "airborne" he meant airborne "all the way," that is, all the way from the reservoir, wherever that might be, to the primary site of lodgment in the tissue. He meant airborne "all the way" and starting from a distance. It was clear that the distance was more than 6 ft, and one dimension was 7 miles, so we are talking about something that starts from 6 ft to 7 miles or more away from the ultimate host and makes the entire journey by air.

Up to this point in considering airborne infection we do not violate the concept by including just any disease that affects the respiratory tract and a number of other systemic diseases that seem merely to use the respiratory tract as a convenience, i.e., as a convenient way of getting into the body. So long as we adhere to *infection*, so far so good, but when we come to consider *disease* as well as *infection*, the "airborne all the way" concept becomes quite limited, for it is impossible within this concept to include most of the common bronchopulmonary diseases of bacterial origin. These have an airborne mechanism, i.e., inhalation in so far as *infection* is concerned, but many of them involve *aspiration* in so far as the transformation of infection to disease is concerned. Thus, if we hold to the "airborne all the way" concept, we are automatically excluding from consideration certain very important diseases of the bronchopulmonary system, notably pneumococcal, staphylococcal, and streptococcal pneumonia; and, indeed, we may be, as Dr. Davenport pointed out, excluding some virus infections if we adhere to the distance from the reservoir as being longer than 6 ft. There is abundant evidence that pneumococcal, staphylococcal, and streptococcal infections do require this aspiration mechanism as well as inhalation.

I use the word "infection" in the strict sense of the term to mean the mere presence of the microbe in the tissues, and by "disease" I mean the reaction or reactions between the tissues and the microbe, the "lesion," if you will.

The question immediately arises whether any useful purpose is served by singling out such a rather mixed bag of diseases as the ones that have only the common property of arising from more than 6 ft away and going the entire distance from reservoir to lesion by the airborne route. The further question then arises whether there is any point in having a conference on the subject.

This is for each of us to decide for himself, but it seems to me that two useful purposes are served by singling out this group of diseases, at least singling them out on an ad hoc basis. First, by so doing we have been able to lure into the study of certain microbial diseases the talents of capable people in physics, meteorology, and other fields, who otherwise presumably would not have become interested in our problems; and second, although we cannot do much about the structure of the bronchopulmonary tract, as such, presumably we could do something about certain other aspects of the airborne chain. These two points, I think, are ample justification for singling out this particular group of diseases. Nevertheless they are a mixed bag of diseases, which means that we have a mixed bag of investigators. This leads to all the problems with which we are familiar, notably, that each investigator is quite aware of the complexities within his own bailiwick and is secure in his belief that the others are entirely innocent of knowledge of any of these

complexities and as a consequence are indulging in dangerous oversimplifications.

A manifestation of this has been that many of you have come to me at one time or another in the past 2 or 3 days and said, "We are not having enough on pathogenesis." I share this interest in pathogenesis. Others have come and said, "We are not having enough about the physical principles; we are having too much on pathology or pathogenesis." The numbers in the two camps have been approximately equal.

As far as pathogenesis is concerned, I believe that I state a conviction held deeply by many of us that the events in the first seconds, minutes, or very few hours are all-important in determining whether infection becomes disease at that particular time and perhaps the course of the disease thereafter.

With today's techniques we cannot study early pathogenesis in the entire bronchorespiratory system without some idea of where "to drill." A part of our difficulty in mutual understanding thus far is that, despite the very great advances that have been made in the physical aspects of these mechanisms, they have provided no real clues as to where to start digging in the tissues for study of that part of the pathogenesis.

With those opening remarks we proceed to some questions designed to see if we have agreement on the terminology and from there to what seem to me to be major topics.

Dr. Cluff, I made a statement on my own concepts of infection and disease, namely, infection being the mere presence of the virus of disease, and disease the tissue reaction to that microbe. Do you agree with that?

DR. CLUFF: Very much so.

CHAIRMAN MCDERMOTT: Is there anyone on the panel who disagrees with that?

DR. FRANCIS: I don't think the mere presence of an infectious agent is sufficient. It seems to me that you must have some evidence of multiplication and establishment rather than just the mere presence of an organism.

CHAIRMAN MCDERMOTT: Do you mean fixed lodgment?

DR. FRANCIS: At least active lodgment rather than just something that is a passive transfer for a matter of some hours.

CHAIRMAN MCDERMOTT: How about disease? Do you approve of the definition of disease?

DR. FRANCIS: That disease is the response?

CHAIRMAN MCDERMOTT: Yes, do you go along with that?

DR. FRANCIS: Yes.

CHAIRMAN MCDERMOTT: Are there other comments on that definition? If not, we can have complete agreement on the question of disease; so far as infection is concerned, it is a question of the degree to which we believe lodgment means that one is a permanent resident, or a reasonably permanent resident, and not a tramp passing through town. Dr. Francis believes we should not count the tramps in our census and should have some evidence of intention to take out citizenship before we call it infection. I believe this point is not a serious one between us.

DR. LANGMUIR: Just a little point here, it seems to me very artificial not to recognize that disease depends on precision of measurement, and that there is a range from manifest clinical illness, where patients are really disabled, to symptoms of something that one can only discern under careful observation. You have to define what you mean by disease in severity before you can reproduce such disease experimentally.

CHAIRMAN MCDERMOTT: As far as the definition is concerned, we defined *disease* as the interaction between the microbe and the tissues. *Illness* is something quite different and has to do with clinical manifestations and their perception by the person. In other words, it is the *lesion* we are talking about right now. Our definition for airborne was 6 ft or more out, and all the way by the airborne route from the reservoir to the initiation of the lesion. Would you accept that, Dr. Langmuir?

DR. LANGMUIR: Yes.

CHAIRMAN MCDERMOTT: Dr. Wood, do you agree with this point and if one uses it as a classification for airborne, what diseases would you say were included or excluded?

DR. WOOD: You have to exclude many of the conditions you mentioned where the infection is transmitted by droplets and the droplets do not travel very far. Included in this category are a number of important respiratory diseases; on the other hand, as you pointed out, there are a number of diseases in which the infecting organisms travel quite a distance by air. Dr. Langmuir listed some. One he did not include in this list, however, was staphylococcal infection. I would like to ask him whether he would not agree that under certain circumstances staphylococcal in-

fections may be airborne, in accordance with the definition which we have adopted.

CHAIRMAN MCDERMOTT: We are talking about *infection* and not *disease* as far as the airborne route is concerned.

DR. WOOD: Yes.

DR. LANGMUIR: Oh, I left out a lot, not just staphylococcus but streptococcus and smallpox under some circumstances, probably influenza and measles. A whole group of disease agents occasionally may get out into the air and spread beyond 6 ft, but this is a 10%, 20%, and maybe up to 50% phenomenon. These infections also spread by contact and it is almost impossible to distinguish the two modes of spread.

DR. DINGLE: Theoretically, is there any infectious disease agent which is smaller than 10 μ that could not be airborne?

CHAIRMAN MCDERMOTT: Airborne all the way to the production of the lesion?

DR. DINGLE: Yes.

CHAIRMAN MCDERMOTT: That leads to a question. Do you believe that we are entitled to consider, in terms of both infection and disease, infection in which the airborne route is a mechanism that occurs *naturally at some time* even though this is not the most frequent way?

DR. DINGLE: I think it is possible that almost any agent causing an infectious disease that you could name could, conceivably, under some circumstances, be airborne under the definition you propose.

CHAIRMAN MCDERMOTT: I am not talking about case reports from the exotic literature but something that occurs as a reasonable probability. Do you think that most of them would be in that class?

DR. DINGLE: Some agents are rather difficult to conceive of as commonly being airborne, for example, infectious hepatitis, but I do not see why even that virus could not be airborne. For instance, flushing toilets, as somebody pointed out, could produce an aerosol of virus which could cause infection.

CHAIRMAN MCDERMOTT: We can conceive that there is no specific biological similarity among a large number of these things, but what we mean by the concept of airborne, at least at the moment, is remote delivery "all the way" by the airborne route, and we can modify that as we go along. At this point, logic might make us wish to go all the way from the reservoir to the final lesion, but a number of the points having to do with the reservoir and with the process of transfer were taken up this morning. The others we will attempt to bring out later. I proceed directly to the question of the process of inhalation and its relation to pathogenesis. Dr. Nelson, during the process of inhalation what are the common points of entry or zones of entry from the respiratory lumen to the tissues, or can any zoning be established?

DR. NELSON: We had this pretty well drawn out for us and it is quite clear that, with certain reservations, we can be rather definite and specific. The general features of particle deposition in the respiratory tract are known and have been outlined here; this applies particularly to the behavior beyond the nasopharynx, although we have a moderate amount of information on particle behavior in the nasopharynx. Inevitably, the site of deposition and subsequent path of the infectious units will play a role in the pathogenesis of the disease.

Now, the point has been made, and it is correct, that the preferred deposition region for particles of the 1- to 5-μ size range is in the deep parts of the respiratory system, whereas particles of above 5 μ, and particularly above 10 μ, are filtered out in the nasopharynx. This does not mean, however, an exclusive fractionation. It is a statistical statement, and some large particles not only can but do find their way into the deeper lung spaces, and some, in fact quite a large number, of the smaller particles are deposited in the upper respiratory spaces.

Now, when this systematic background is correctly applied to the design and analysis of an experiment in airborne infection, of which Dr. Tigertt gave us a good example, the response is so in accord with prediction that it would be farfetched indeed to go beyond this as a basis for explanation of the results.

CHAIRMAN MCDERMOTT: In other words, you think Dr. Tigertt's data in those particular circumstances meant that the large particles landing up high were probably not important?

DR. NELSON: Yes, that is correct. It seems quite likely, however, that there are a number of organisms which have their preferred points of entry in the upper parts of the respiratory tract, and Dr. Davenport gave us a lucid explanation of mechanisms whereby organisms deposited there could overcome local defense and produce infection.

The point made by Dr. Wright regarding the

retrograde movement via aspiration of material present in the upper part of the respiratory tract into the deep parts of the lung also must be kept in mind as a mechanism for redistribution of deposited material.

CHAIRMAN MCDERMOTT: So that, in so far as the distribution of particles is concerned, we have a certain amount of information of a physical sort, and we have biological confirmation of some of that information by virtue of the Tigertt studies. Beyond that, though, we cannot be very precise as to what is the preferred route.

DR. NELSON: I emphasize the fact that there is a large body of information one can call on both to establish hypotheses and to guide experiments in this field. The fields of respiratory physiology and aerosol physiology have built a solid body of information which can be utilized in devising additional experiments to clarify these problems.

CHAIRMAN MCDERMOTT: From what you said, we do not have, except in so far as we have specified from this body of information, the tips we would like to have as to where to start to make more intensive studies of early pathogenesis.

DR. NELSON: I think if we look at each specific disease we may find such clues.

CHAIRMAN MCDERMOTT: You may find these leads from other than what we might call statistical abstractions.

DR. NELSON: Influenza may be a good example; here is a disease predominantly of the upper respiratory tract, and it is logical to look for points of entry in this part of the system. I think it would be very useful to carry out studies with particles of large enough size to have a very low likelihood of entering the lower system to see whether or not this presumed point of entry is the effective one.

CHAIRMAN MCDERMOTT: You also made the point that the larger particles, as Dr. Wright pointed out, can get down into the lower respiratory tract, perhaps not entirely by the airborne mechanism but by the equivalent of aspiration mechanism. This introduces the question of the cleansing mechanisms in the lower respiratory tract and the relation of those to the upper. Dr. Wood, do you want to talk on that point? How secure can we feel, for example, that we have identified the cleansing mechanisms of the alveolar system?

DR. WOOD: I think the best way to start this part of the discussion would be to ask Dr. Wright to translate the diagram before us (Fig. 1).

DR. WRIGHT: We have been looking at thick lung sections and making three-dimensional reconstructions recently, and we are aware of the current terminology in characterizing the branchings of the bronchial and alveolar systems. The figure that I have drawn is, of course, completely schematic and no attempt will be made to give comparative dimensions.

As one proceeds distally along the tracheobronchial system, each new order of branching is somewhat smaller in diameter than the one from which it arose. Gradually the cartilages become less complete and ultimately disappear. Bronchial glands, which are very plentiful in the trachea, become fewer in number as do also the goblet cells. The ciliated epithelial cells become slightly less tall and there is much less stratification of the mucosal epithelial cells. Ultimately, one or more orders of bronchioles are reached that have no bronchial glands and few or no goblet cells. Ciliated plus nonciliated cuboidal cells comprise the lining. This order of branching, having no mucous glands or goblet cells, is termed the terminal bronchiole because the next division is characterized by the first appearance of alveolar structures. Arising from the terminal bronchiole are two or more orders of branching characterized by the presence of fully developed alveoli scattered in the wall, usually on one side only. Ciliated cells are few in this order of branching and the epithelium tends to be cuboidal. These first alveolus-bearing branches are termed respiratory bronchioles. The next one or two orders of branching have more numerous alveoli scattered around the entire circumference and are referred to as alveolar ducts. Each alveolar duct opens into a space termed the atrium, from which arise two or more saccular structures made up of alveoli. Beginning in the alveolar duct, the cuboidal epithelium becomes flat and no cilia exist. As one proceeds into the atrium and into the alveolar areas, the epithelium becomes quite flat. This diagrammatic representation is in a single plane and is virtually never seen in toto in a single microscopic section of the lung. Actually, in three-dimensional reconstructions it can be seen that once the respiratory bronchioles are reached, subsequent divisions may arise at any angle. An alveolar duct may abut on one of its own clusters of alveolar sacs or may border alveoli from a sister respiratory or alveolar duct.

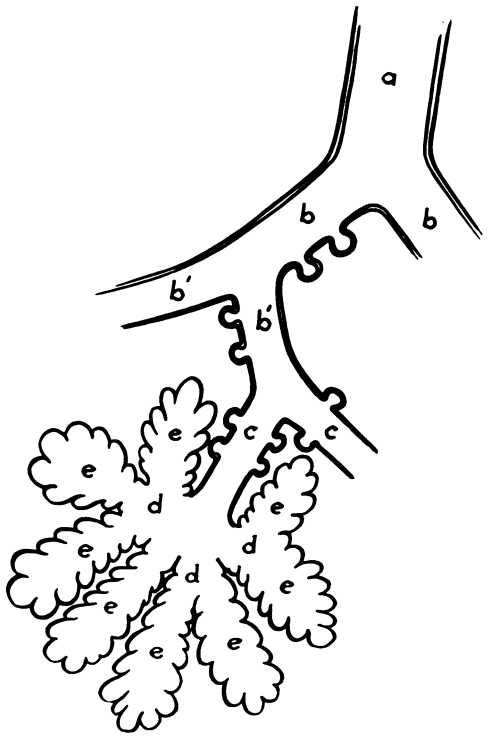

FIG. 1. *Schema of distal respiratory unit. a = Terminal bronchiole; b = respiratory bronchioles; c = alveolar duct; d = atrium; and e = alveolar sac. (Drawn on blackboard by Dr. Wright.)*

Several times during the course of this Conference, the question has been raised as to where lymphatics are found within the lungs. Miller (10) describes the lung as being abundantly supplied with lymphatics and indicates that these channels are found coursing along bronchi and blood vessels throughout the lung with the exception of the walls of the atria and of the alveolar sacs. In general, they appear to extend into all portions of the lung where the bronchial arteries go. Because of the intimate way in which alveoli abut upon the larger conducting tubes of the lung, one can say that in all parts of the lung there is very little distance between alveolar walls and lymphatic channels. If one believes that particles either free or engulfed in macrophages are capable of passing through the limiting membrane of the alveolus, one can just as easily believe that they will pass through a second membrane. There are, therefore, abundant lymphatics into which materials may lodge.

The only other comment I would make is that the noncilia-bearing area distal to the terminal bronchioles appears to be most active from a cellular point of view. Kleinerman's (7) experiments with nitrogen dioxide, which can be assumed to have injured the cells throughout the tracheobronchial alveolar system, show that the most intensive activity develops in this region. For example, within 2 hr after exposure to nitrogen dioxide, he found the basement cells of the respiratory bronchioles to be reduplicating to replace those that have been injured. Instead of reduplicating to produce a single layer, the mucosal surface rapidly becomes three to four cell layers thick and one has the impression that a polypoid structure develops, which surrounds and engulfs the debris consequent to previous injury. Within a matter of a few days, the structures revert to their normal single-cell depth. It appears that this region is anything but a passive sort of well-defined structure which remains the same all of the time.

CHAIRMAN MCDERMOTT: And is that area contiguous to alveoli?

DR. WRIGHT: Yes.

CHAIRMAN MCDERMOTT: Is that the same area that Dr. Nelson was talking about?

DR. NELSON: I am not sure Dr. Wright and I agree on the size.

DR. WRIGHT: I do not know. I was surprised that you drew the particles as being settled out, and that is why I asked you: Have you seen them there? You tell me you have not.

DR. NELSON: No, this concept is inferred from the very high concentration gradient present at this particular front.

DR. WRIGHT: I would say that they must be there; but I am not prepared to say they are at (*c*) and not at (*b*), or not at the atrium.

DR. NELSON: Dr. Wright, I think you will agree that one finds a high gradient at the interface.

DR. WRIGHT: I think that the alveoli do little expanding.

DR. FRANCIS: The making of room to take in new air is probably proximal to the alveolar structures. It is much more likely to be out where you say there are only 700 ml of directly interchangeable air in quiet breathing, and that would put it well proximal to large clusters of alveoli.

DR. NELSON: I do not think we have the detailed knowledge to reach a conclusion at this time.

DR. WRIGHT: Professor Hatch, how is it that we see, and I know we do see, particles in the alveoli; how do they get in there? These are inanimate particles.

PROF. HATCH: There is the statistical possibility that some of the alveoli are hanging down so that particles can settle out by gravity. There is no doubt, however, but that we will see more particles of finer size in the alveoli.

DR. DINGLE: Where do you see the maximal deposition of particles?

DR. WRIGHT: I can't answer that. I don't know that it has much relevance, because over a long period of time these particles may appear almost anywhere. Macrophages pick them up and move and discharge them. It has been shown that particles are constantly undergoing turnover and redistribution. This goes on in structures that we have thought of as being quite inactive, i.e., a silicotic nodule. Apparently the particles move from the center to the periphery. Now, I have not had a chance to see any of the autographs done of lung tissue after inhalation of radioactive particles. Professor Hatch, did you see any of the autographs done with radioactive material?

PROF. HATCH: Yes.

DR. WRIGHT: Did they give any idea of where the deposition was?

PROF. HATCH: I don't think so.

DR. WRIGHT: After the lapse of time the particles were all mixed in together. It would be worth-while to see if we could identify where particles would be placed with a single breath. Technically, there are many difficulties.

CHAIRMAN MCDERMOTT: Dr. Wood, are you ready to answer the question?

DR. WOOD: There is one anatomical point which remains unsettled. It has to do with the question whether or not the alveoli are lined with squamous epithelium which represents an extension of the epithelial lining of the bronchi. There is no doubt that there is a cellular lining on the air side of the alveoli. The real question has to do with the nature of the cells which make up this lining. Dr. Clayton Loosli (2, 6, 8), who has been interested in this problem for many years, believes that the alveolar lining cells are "septal cells" which belong to the reticulo-endothelial system and, therefore, are actively phagocytic. William Snow Miller (10), on the other hand, took the position in his classic monograph on the anatomy of the lung that these cells are of epithelial origin and nonphagocytic. I don't believe that this difference of opinion has yet been completely resolved (9).

There are one or two things to add about the mucociliary escalator of the respiratory tract. Dr. Bang described its function in the upper respiratory tract. Its role in the lower tract has also been thoroughly studied. In 1941, Dr. O. H. Robertson of the University of Chicago published a splendid summary (11) of the work done up to that time on the defense mechanisms of the respiratory tract. Among the experiments reviewed were those of Barclay (1), who blew a radiopaque lead powder down the trachea of dogs and studied its removal by means of X-ray films taken at frequent intervals. He clearly demonstrated by this technique that the particles remain in the bronchial tree for only a relatively short period of time because of the action of the mucociliary escalator, which carries them upward to the pharynx where they are finally swallowed. Indeed, practically all of the particles are gone from the bronchi by the end of 24 hr.

Quantitative measurements have been made of the speed with which the mucous blanket moves in different parts of the bronchial tree. In the lower regions where the bronchi are smallest, the motion is relatively slow, but further up toward the oropharynx the escalator moves faster and faster until the mucus finally reaches the oral cavity.

CHAIRMAN MCDERMOTT: Would you relate that to alveolar cleansing?

DR. WOOD: The relationship is indicated by Barclay's second experiment with the lead glass powder, this time suspended in syrup. Instead of blowing it into the trachea of the dog, he allowed it to dribble down the bronchial tree. In this liquid form, of course, it went all the way down into the alveoli where it remained for weeks rather than hours. This demonstration illustrates very nicely how slowly the cleansing mechanism operates at the very periphery of the lung as compared with the extraordinarily efficient escalator system in the bronchial tree.

As for the cleansing mechanism in the alveoli, it is generally agreed that the "dust cells," which are nothing more than macrophages in the alveoli, are directly involved in removing foreign particles from the terminal air sacs. It is thought that the dust cells, which phagocytize foreign

particles, are eventually carried back far enough into the bronchial tree to be picked up by the lymphatics and thence taken to the hilar lymph nodes. This is a very slow process in comparison to the bronchial escalator, which moves relatively rapidly.

If a particle succeeds in reaching an alveolus and, in setting up a sufficient amount of irritation, its presence calls forth an acute inflammatory response during which polymorphonuclear leukocytes rapidly enter the alveolus and take over many of the phagocytic functions of the macrophages.

The polymorphonuclear leukocytes, however, have a very short half-life; they are expendable cells which disintegrate relatively rapidly after they have done their phagocytic job. The debris resulting from their disintegration is taken up by the macrophages and finally carried away by the lymphatics.

This is a very quick summary of the general concepts of the cleansing mechanism held by most pathologists. I am sure that the story is incomplete as I have related it and that we will eventually find out that there are many other factors involved. One has already been suggested in this Conference, namely, that there is probably an important substance lying on the surface of the cells which line the alveolus. The characteristics of this inner coating and its possible role in the alveolar defense will be extremely interesting to study.

CHAIRMAN MCDERMOTT: Does it seem that the microbes that get into the alveolus are either destroyed there by phagocytosis or carried from there to the lymphatics by the mechanism you have outlined and that which Dr. Albrink mentioned regarding his studies with anthrax?

DR. WOOD: Certainly these are the principal mechanisms that the investigator can witness. There may be others as yet unrecognized.

CHAIRMAN MCDERMOTT: Dr. Nelson was telling us about large particles getting into the alveolus possibly by aspiration, and you described the ingress particles of lead powder, too. How does the system get blocked?

DR. WOOD: Do you mean from the alveolus back to the regional lymph nodes?

CHAIRMAN MCDERMOTT: Yes. How is this mechanism suppressed?

DR. WOOD: I think there are at least two ways in which the cleansing mechanism may be suppressed. One involves the presence of water (or edema) in the alveoli, which decreases the efficiency of the phagocytic mechanism. This is an important factor in the pathogenesis of certain bacterial pneumonias. The experiment of Harford and Hara (5), in which fluid in the alveoli made the mouse lung highly susceptible to inhaled pneumococci, is a case in point. Secondly, there is the possibility that Dr. Middlebrook referred to, namely, a breakdown of the drainage mechanism to the regional lymph nodes.

Two alternative explanations have been offered for such a breakdown. One was based on an anatomical blockage of the lymphatics (Dr. Albrink) and the other on the failure of macrophages, which had ingested virulent organisms, to migrate from the alveoli to the lymphatic channels (Dr. Middlebrook).

CHAIRMAN MCDERMOTT: Acute processes, such as edema, some chronic underlying disease, or a response to the microbe itself, are all possibilities whereby these cleansing mechanisms can be suppressed.

Now, Dr. Langmuir, you wished to make a comment on this anatomical problem.

DR. LANGMUIR: I want to know the origin of the mucous blanket. Professor Hatch has given us the idea that it dips right down into the alveolus and even pulls particles out because of its tenaciousness. It has to come from somewhere. A related point is the aspiration of mucus. Does this not have an intrinsic surface tension and viscosity and thus lead to a plug somewhere up the line with maybe atelectasis developing behind it? Does aspiration really take the microbes to the alveolus or lodge them at a higher level in the bronchus where there is the ciliary cleansing mechanism?

DR. WOOD: I think both of these things can happen, depending on the viscosity of the material aspirated. There used to be, as you know, Dr. Langmuir, a theory that acute bacterial pneumonia did not occur without atelectasis. The evidence today in favor of this concept is not good. It is possible, for example, to produce pneumococcal pneumonia in mice by merely injecting some sterile serum into their lungs and then exposing the mice to an aerosol of pneumococci. No bronchial plugging is involved in such an experiment. This, of course, does not mean that pneumonia cannot occasionally be caused by an infected plug of mucus in a bronchus. The

mucus which comes from the goblet cells in the mucous membrane lining the respiratory tract is a relatively good culture medium for bacteria.

DR. LANGMUIR: How far down do the goblet cells go?

CHAIRMAN MCDERMOTT: To where alveoli bud out.

DR. WRIGHT: As I recall, they are relatively few the farther down you go.

CHAIRMAN MCDERMOTT: They go down as far as where the first chambers start budding out.

Now, in terms of attempting to relate pathogenesis to aerodynamics, based on what we have discussed in these days of conference, what is our need for further studies in pathogenesis? Where do we stand? Could you start on that, Dr. Wood?

DR. WOOD: On several occasions during this Conference, the question has arisen whether an organism which lodges and remains in the upper respiratory tract can produce disease or whether it must always penetrate the lower respiratory tract to cause overt illness.

CHAIRMAN MCDERMOTT: In other words, how do we integrate what you have been talking about with Dr. Nelson has been talking about?

DR. WOOD: I think that we might settle this question for certain microbial species by artificially separating the upper and the lower portions of the respiratory tract and then exposing one or the other to the test organism.

I wonder if this could not be done even in man with a properly designed tracheotomy tube. If such a tracheotomy tube had a suitable diaphragm, theoretically it would be possible to expose only the lower part of the respiratory tract to *Coxiella burnetii*, for example, and then in a similar experiment expose only the upper part. It is conceivable that in this way one could find out whether the Q fever organisms can actually get into the blood stream from the upper respiratory tract as well as they can from the lower, or vice versa.

This is, of course, purely an arm-chair suggestion, but an approach of this general nature might make it possible to determine the real portal of entry in a number of airborne infections.

CHAIRMAN MCDERMOTT: Without saying that we have necessarily gone as far as we can go with the present techniques, do you think the time has now come to try to divide the respiratory tract for more pointed studies?

DR. WOOD: I believe it might be worth trying instead of relying wholly on the approach of varying the particle size.

CHAIRMAN MCDERMOTT: And to depend to such a great extent upon statistical probabilities as to where various lodgments occur.

DR. WOOD: Perhaps you could get some meaningful answers by varying the particle size; but not being a very good statistician, I would prefer, if possible, to design a more direct experiment.

CHAIRMAN MCDERMOTT: This does represent one point on which we have been focusing. Dr. Albrink really raised two concepts. One was that the alveolar cleansing mechanism might be suppressed by chronic structural changes in the lung, and the other was that, by virtue of that alteration, the nature of the subsequent disease might be changed. These considerations raise the question of portal of entry. Dr. Dingle, how do we feel about the relation of the portal of entry to the nature of the subsequent disease?

DR. DINGLE: It has always seemed to me that certain of the diseases we are discussing have characteristic patterns. Those patterns were recognized and described long ago in many instances. If agents of one of these diseases enter the body, establish themselves, and multiply, they are ultimately going to reproduce the pathogenesis of that disease, regardless of the portal of entry. Therefore, I think that the portal of entry may alter the initial characteristics of the disease, but it is not going to change the ultimate course of the disease.

CHAIRMAN MCDERMOTT: Could we divide our portals into two? One is the systemic disease in which the portal of entry happens to be the lung but it could be the blood stream or some other way. In such cases, I judge, you believe that it does not matter how the microbe gets in. You could put it in the left ear. As long as it gets in somehow, it will end up the same way.

DR. DINGLE: I think that if you introduced, for example, the rickettsiae of Q fever into the nose and confined the portal of entry to the nose, ultimately Q fever would develop which could not be distinguished clinically in its manifestations and its course from an infection initiated by putting the rickettsiae in the lungs or injecting them subcutaneously, intravenously, or however. Dr. Tigertt indicated that quite clearly.

CHAIRMAN MCDERMOTT: Now, do you believe that this principle likewise applies to diseases of the bronchopulmonary structures?

DR. DINGLE: Yes, I see no reason for them to be different from any other diseases.

CHAIRMAN MCDERMOTT: In other words, you believe that meningococcus and pneumococcus have good reason for their names.

Then, in a sense why do we care about what Dr. Wood and Dr. Nelson have been talking about?

DR. DINGLE: I do not think we do. I do not think it matters a bit.

DR. WOOD: I think it matters in terms of how a disease is naturally acquired. Take Q fever, for an example. If you swab enough *Coxiella burnetii* onto the mucous membrane of the nasopharynx, conceivably you may produce the disease Q fever, but this does not tell you how Dr. Tigertt produces it when he blows only ten organisms at the host.

DR. DINGLE: How do you know that one of them does not lodge in the nose?

DR. WOOD: It seems to me that the natural portal of entry is something worth knowing about, particularly in relation to transmission. Even if it is admitted that Q fever may be artificially produced through either the lower or upper respiratory tract, it is still important to find out precisely how it is acquired in nature.

CHAIRMAN MCDERMOTT: And we may have gone about as far as we can go with the approaches used. Is there any agreement on that one or not?

DR. NELSON: I think the portal of entry does matter and point out that we have to define actual entry points to devise adequate control procedures.

DR. DINGLE: Matter for what? Does it alter the subsequent course of disease?

CHAIRMAN MCDERMOTT: No, the nature of this ultimate disease.

DR. DINGLE: I do not think it matters.

DR. NELSON: I thought you had gone beyond this and applied "does it matter" to the whole question. I think it matters greatly.

CHAIRMAN MCDERMOTT: We were asking, is it conceivable that the ultimate nature of the disease is altered by the portal of entry?

DR. DINGLE: I do not know of such evidence.

DR. CLUFF: The character of disease may be influenced by the portal of entry. For example, as illustrated during this Conference, induction of disease in experimental animals by intravenous inoculation of influenza virus results in alveolar lesions not seen in infection induced by the respiratory portal of entry. In addition, we have been told that bacteremia is common in bubonic plague but uncommon in pneumonic plague.

DR. DINGLE: I do not think that necessarily follows unless you can show that the pneumonia that follows a local lesion in plague or tularemia, for example in bubonic plague or the oculoglandular type of tularemia, is different from the pneumonia following some other route. For example, can a pathologist examine pneumonic lungs and say that obviously this pneumonia came from a "bubo," whereas that one came from the air?

DR. CLUFF: I agree that if *pneumonia* results from infection, the pulmonary disease may be the same, irrespective of the portal of entry. The distribution of lesions in the lung may be different, however, if the pneumonia is induced by inhalation of the microorganism or by bacteremia.

DR. FRANCIS: In these situations you obviously have very distinct differences, but I think that the last question is part of the whole situation. When you say "all the way," what do you mean? Are you talking only about pneumonic infection or are you talking about respiratory infection, or airborne infection, and if you are going to limit "all the way" to something that has to be down in the alveoli, then I think we are in an impasse.

CHAIRMAN MCDERMOTT: I said from the reservoir to the lesion.

DR. FRANCIS: You said, "all the way," and I still have a little difficulty believing the size of the particle to be such a complete determinant of the rest of the behavior of the agent. Dr. Wright's picture of all these ramifications certainly indicates much difference, I think, in the pressure dynamics of what it was possible to do and how far it was possible to push organisms just because of a certain size. I suspect that they have the opportunity to fall out. I emphasize again as far as influenza is concerned that the alveolus is not primarily of great importance in the establishment of the original illness or the original lesion.

In the case of Dr. Tigertt's study with Q fever, the alveolus serves as a very effective portal of entry for the agent but is not a very important factor so far as the production of Q fever is concerned. We discussed one instance where Q fever can be produced by the subcutaneous rather than through the intranasal route. Influenza cannot be produced by other routes than the intranasal except under special conditions, whereas one can

produce it easily by the intranasal route. It does not start at the alveolar level, so its pathogenesis is not merely a matter of the anatomical factor or the physical factor or air flow, but rather the biological features of the agent are very important factors in determining localization and initiation of infection. Dr. Middlebrook said that when he used virulent tubercle bacilli, they stayed in the macrophages in the alveolus and did not seem to move for weeks, but that when he used the avirulent BCG, they were taken to the lymph nodes and stayed there. Obviously there are different mechanisms involved in those two phenomena so far as tuberculosis is concerned.

I believe we must obtain more information about the different specific phenomena at different levels and to define our terms.

CHAIRMAN MCDERMOTT: By different levels do you mean different scientific levels or different respiratory levels?

DR. FRANCIS: I mean levels of seeking information. For example, I mentioned the fact that an organism gets into the lung or terminal bronchiole or alveoli, multiplies, and inflammation starts. This is certainly an important part in determining what happens, and I do not think it depends merely on the size of the infecting particle.

CHAIRMAN MCDERMOTT: To sum up this part of the discussion, we have a certain amount of information on the dynamics of the situation. This information has been extremely valuable to us and has, in a sense, as Professor Hatch keeps emphasizing, pointed out what is the *usual* happening for most cases but not necessarily what happens in every case.

Then we have the beginnings of biological confirmation of certain aspects. We have the Tigertt data on the one hand, we have the points that Dr. Nelson was making, and we have the observations by Dr. Wright, who is beginning to feel that a particular portion of the lower bronchiolar system is a very reactive area. We have the sort of phenomena that Dr. Middlebrook reported. We are now attempting to reconcile in some way not facts *but places to look for facts* and to judge in some way where is it profitable to keep going and where are we just spinning our wheels. Dr. Wood suggested that it occurred to him to attempt to separate anatomically divisions of the respiratory tract and then to try studies of the type we have been reviewing.

DR. FRANCIS: Professor Hatch, is the picture of pulmonary involvement produced by tin fumes quite different from that produced by particulate materials? From my understanding of this, tin is in vapor form and the metal gets crystallized in the lung and stays there for indefinite periods. Is that still at the terminal bronchiole? It is certainly not the type of material that gets centralized in the lymph nodes, is it?

PROF. HATCH: I have no first-hand information, but as one can see in a chest X-ray, the dust is very generally distributed throughout the lungs.

CHAIRMAN MCDERMOTT: That does raise a question that came up in this morning's discussion: To what extent do all of the irritants and accessory materials that accompany the microbes play a role in the determination of infection, in the determination of the early pathogenesis of disease, and subsequent events? Some of these matters have been discussed with respect to the possibilities of mucus, but we were reviewing the question of antigens, antitoxins, and other materials. We certainly are inhaling all sorts of things along with them. Dr. Cluff, do you want to start?

DR. CLUFF: Most of the work presented during this Conference has dealt with infection in the normal or unaltered host. There are circumstances, however, in host resistance in which alterations, attributable to local or systemic factors, may be important determinants of susceptibility to infection and of the characteristics of the disease induced. A few illustrations of the influence of such factors upon airborne infection were alluded to during the Conference. Dr. Furcolow, for example, indicated that persons hypersensitive to histoplasmin may develop quite a different disease than normal nonhypersensitive persons upon exposure to histoplasmosis. In addition, Dr. Albrink mentioned the possible influence of coexistent sarcoidosis upon the characteristics of anthrax in one of his patients. Furthermore, Dr. Eichenwald has demonstrated the probable importance of coexistent viral respiratory disease upon infection by and dissemination of pathogenic staphylococci.

It is interesting to speculate upon the implications of what Dr. Wright had to say about the production of inflammation of the respiratory bronchioles by inhaled nitrogen dioxide. Nitrogen dioxide is a common part of air pollution, and it is possible that it could influence significantly the

susceptibility of the respiratory tract to infection by inhaled microorganisms.

Dr. Bennett raised the subject of the deleterious influence of endotoxin upon the respiratory tract, and there is a great deal of work indicating that endotoxin can affect the evolution of a microbial disease. The inhalation of substances possessing endotoxin activity could have a profound influence upon the occurrence and course of experimental or naturally acquired airborne infection. Consideration of these effects of endotoxin and other irritating or toxic substances upon the evolution of infection should be included in any experimental work of airborne infection. For example, challenge of human beings or experimental animals with microorganisms in egg-slurry, broth, or other substances could conceivably influence the outcome of infection by nonspecific effects upon host resistance.

It is desirable that further studies be performed to evaluate the effect of factors influencing resistance to airborne infection.

CHAIRMAN MCDERMOTT: Are you introducing another factor into the common question of the mechanics of airborne and aspiration disease of the bronchopulmonary structures and the systemic diseases arising therefrom?

DR. CLUFF: Yes, an obviously important factor influencing the response of the respiratory tract to infection is the structure of the bronchopulmonary tree. For example, obstruction of the bronchi or trachea may be a determinant in the occurrence and course of respiratory infection. In addition, Dr. Bang has indicated that changes in mucociliary function of the respiratory mucosa can have a deleterious influence upon the evolution of an infection.

CHAIRMAN MCDERMOTT: If we are to find out more about early pathogenesis, we have to consider what we can learn from aerodynamic studies as to why these events happen, in what form the agents are presented to the respiratory tree, and what we know about the cleansing mechanisms. We further have to take cognizance of the fact that, in all such studies, what might be called a normal cleansing mechanism cannot be counted upon as completely unaltered in many people, plus the fact that the microbe coming in may carry its own antigens with it. Thus, if we are to progress, we need more studies involving all three of those parameters.

I might ask Dr. Glassman whether he agrees that this position has developed out of this Conference, and is there anything in the type of study which he has been doing which could be further defined?

DR. GLASSMAN: I agree with this point and would take this opportunity to add that I think the development of apparatus and techniques for creating homogeneously sized aerosols does provide a very adequate opportunity for carrying forth many of these studies.

CHAIRMAN MCDERMOTT: Do you think that more attempts should be made to direct aerosols to various segments of the bronchopulmonary system?

DR. GLASSMAN: Certainly this would provide more effective information on the role of the respiratory tract as a portal of entry in experimentally induced or naturally acquired airborne infection.

CHAIRMAN MCDERMOTT: We are always going to be up against Professor Hatch's point until we do something like that.

DR. GLASSMAN: The present approach is completely on a statistical basis.

CHAIRMAN MCDERMOTT: So, if there is anything to the notion that the ultimate course of the disease is affected by what happens at the immediate portal of entry, then such studies would be of even greater importance and in any case important in early pathogenesis. Dr. Andrews, how do you feel about this as a concept?

DR. ANDREWS: You mean as a logical way to proceed? There is always the possibility of abnormal structures, I suppose, to deal with in the first place, but I do not know how you prevent or avoid them; but certainly, with the primary site of the lesions presumably in the terminal sections of the bronchiole, I think these should be the areas of intensive study.

CHAIRMAN MCDERMOTT: What types of apparatus do we need? One would be, as Dr. Glassman suggested, apparatus that would give us particle sizes of a more uniform nature. How about directional methods? On what types of problems do we need technical assistance?

DR. GLASSMAN: One could summarize the present situation as follows: current technology is completely adequate for deriving homogeneously sized microbial aerosols. The aerosols can be controlled to provide predictable contents as dilute as one organism per liter of air. These techniques have made possible investigations in

man such as those reported at this Conference by Drs. Tigertt, McCrumb, and Saslaw.

Techniques requiring development are those of a surgical or pathophysiological nature which would permit study of individual segments of the bronchopulmonary system in relation to airborne infection. It would also be very desirable to have improved techniques for controlling the numbers of organisms per particle in experimentally produced aerosols.

DR. CLUFF: One other question: how well can we equate studies on aerosolized-induced infection of experimental animals with what we might anticipate to be the case with a human being?

DR. DINGLE: In general, I think we cannot extrapolate from animals to man. The only example we have where this relationship has been demonstrated is in the work of Dr. Tigertt and his associates on Q fever.

CHAIRMAN MCDERMOTT: Do you agree with that?

DR. FRANCIS: Yes, I think this is a very excellent area for study. In other words, if one is going to try to equate with the human spreader and transmission to man, should not more attention be given to the dispenser and how he distributes his organisms to another man or to a suitable agent?

CHAIRMAN MCDERMOTT: Let me emphasize at this point that we have left the question of the process of inhalation and are now considering other aspects of the total chain, namely, the reservoir and the process of transition or travel.

DR. LANGMUIR: I agree with the general statement that we must not make the translation from animal experiment to man in one seven-league boot step, and we have a few brilliant examples such as the overgeneralization of the nasal portal of entry for poliovirus and how it held up advances in that field; but when the animal work is well done and intelligently interpreted, a direct translation is nearly always possible. We have just gone through a phase in poliomyelitis research where the neuropathogenesis of attenuated strains in monkeys was doubted by many investigators to be significant but it now is turning out to be most important. In general, I think we should interpret our animal observations far more broadly than we now do, rather than the reverse.

CHAIRMAN MCDERMOTT: I gathered from Dr. Davenport yesterday and from other discussion that as far as reservoirs of influenza are concerned, for example, and leaving aside the question of where was the ultimate transfer, not too much is known about exactly how dissemination takes place.

DR. FRANCIS: I think it depends largely on how conservative one is in his acceptance of data.

CHAIRMAN MCDERMOTT: Do you think more should be done?

DR. FRANCIS: It seems if one considers nothing but the ferret and hog data, the distribution of virus is certainly not by rubbing noses.

DR. ANDREWS: May I amplify what I said by raising a question? Accepting the fact that the terminal ampullae should be the object of further study, are these the only sections of the tracheal tree that merit attention from the standpoint of explaining these processes?

CHAIRMAN MCDERMOTT: My understanding was quite the reverse, Dr. Andrews. It seems to me that we have established a fairly general consensus that all parts of the tracheobronchial tree should now be studied. We have full realization of the point raised by Dr. Dingle that just by forcing a thing into a place does not prove a great deal, and we should continue the major attempt to establish what are the natural methods of infection. To some extent the aerodynamic approach, which has been extremely stimulating and productive, does not seem to be leading into a next stage as far as pathogenesis is concerned, and we ought now to think in terms of varieties of zones and levels and try to find out all we can about them.

DR. NELSON: I think you are going a little too far, from my view. I think that the aerodynamic approach has not been fully exploited. Dr. Wood's suggestion is an excellent one, and I would like to record that the use, for example, of homogeneously sized particles of known bacterial content has not been fully exploited.

CHAIRMAN MCDERMOTT: In what direction do you think it could be further exploited?

DR. NELSON: I think fuller experimental use could be made of the controlled variation in the particle size of the infective units to which the human experimental animal or the laboratory experimental animal is exposed. It has been done beautifully in a few instances.

CHAIRMAN MCDERMOTT: Do you think that more diseases should be studied in this way?

DR. NELSON: I merely interjected this com-

ment because I wanted to avoid the implication that this approach had been exhausted.

CHAIRMAN MCDERMOTT: Do you see any new directions for this type of approach?

DR. NELSON: I would rather not pursue this question too far. I think it is fairly apparent what can be done. Various procedures have been used; they are readily available. Although some others are not published, I understand they are about to be reported.

DR. CLUFF: May I make a suggestion of an important approach to improve our understanding of the aerodynamics of airborne infection? It was indicated previously that the number of infecting units within an airborne particle is important. For instance, how many bacteria are there within a particle of 15 μ as opposed to a particle of 5 μ in diameter? When we consider only particle size, we are not considering the unit specifically responsible for initiating infection.

CHAIRMAN MCDERMOTT: Dr. Glassman gave us some data on the subject of the decay or survivability of certain microbes in certain conditions. Dr. Dingle, you were raising a question yesterday about this very matter of survival of the microbes in the particles with specific reference, I believe, to plague. Do Dr. Glassman's data answer your question, or do you wish to explore further?

DR. DINGLE: I was very much interested in Dr. Glassman's data, and I think they showed a longer half-life than any data that I have seen previously, but Dr. Glassman made essentially the point I was trying to make, that viability of the organisms and the length of time they remain in the state where one can detect them by cultivation is only one aspect. The other is the capacity to infect. He pointed out that both drop with time. I think the important criterion is the measure of infectivity and not of mere viability. This is the key to the interpretation of this whole problem.

CHAIRMAN MCDERMOTT: We have a further problem with viability in that if we can see that something is alive, we can say so confidently, but we cannot always say with certainty that something is *not* alive; therefore, we use the terms culturability, viability, and infectivity. We really have three quite different points here.

DR. GLASSMAN: I agree heartily with Dr. Dingle on the importance of determining infectivity as well as viability of microorganisms after residence in the aerosol state. The example of *Pasteurella tularensis* which I cited was chosen on a conservative basis to exemplify one of the more fragile organisms. Data exist indicating that other species of organisms retain both viable count and infectivity in the same ratio for long periods of time.

DR. DINGLE: I do not doubt that, but if we are to understand the respiratory transmission of pneumonic plague, if it is a respiratory transmission, then we have to know something of how long organisms expelled in the air will maintain their infectivity, whether they grow or not, or are alive or dead. If they can infect, then we should have less difficulty trying to explain the transmission.

DR. GLASSMAN: With reference to the point that Dr. Cluff made a moment ago, both particle size and numbers of organisms are important. We can now rather readily control particle size, which in turn aerodynamically determines the site of deposition. What we find rather difficult to do with a great deal of predictability is to control the number of organisms in the larger particles.

CHAIRMAN MCDERMOTT: So that, without prejudice to other aspects of your aerodynamic approach, it seems that there is need for more study of the viability, latency, infectivity, and other biological characteristics of the agents in these particles.

Dr. Langmuir, what do you think has been developed here in the past days or from general knowledge about the immediate conditions of infection, as Dr. Riley has discussed, the sanitary environment.

DR. LANGMUIR: I think that was covered this morning quite well. The various experiences that we now reasonably classify as airborne seem to be rather restricted in many cases. I heartily agree that we should look at these situations far more completely than we yet have for leads as to what were the critical events when these epidemics occurred. I differed with Dr. Riley this morning on this point. It seems to me that to say there was a certain average over the period of his experience is to miss the real gold nuggets. It seems clear that only during certain minutes of certain days during this whole period of time, maybe only 20 or 30 occasions altogether, were his patients distributing organisms. He

should try to identify these special occasions and find the dangerous disseminator. When a really good prospect of a spreader is found, the patient should be made to do a series of relatively simple things like hissing, singing, and reading out loud. The colony of guinea pigs should be exposed for short periods, only a day or perhaps only an hour. I think there are enormous opportunities here.

CHAIRMAN MCDERMOTT: Let me ask you just for the record, Dr. Langmuir, do you believe that the concept of the dangerous disseminator of tubercle bacilli is established, or is it only a concept?

DR. LANGMUIR: Oh, it is established without question. Some epidemics, such as those described by Gedde-Dahl in Northern Norway (3, 4), to me utterly establish the point that during an interval of not more than 1 hr, half a dozen or more primary infections were induced. These were traceable to one open case. What more do you want?

CHAIRMAN MCDERMOTT: That is a special case.

DR. FRANCIS: Is it the person or is it a particular strain of the bacillus that is important?

CHAIRMAN MCDERMOTT: Or is it the conditions under which the transmission occurred?

DR. DINGLE: Or the stage of the disease?

CHAIRMAN MCDERMOTT: Yes. It might be smoke of a peculiar character in a particular smoke-filled room which might turn any one of us into a dangerous disseminator, or it may be that only certain people are the dangerous disseminators. Do you think any of these concepts are established or are they working hypotheses?

DR. LANGMUIR: They are sharply enough defined to warrant a great deal of effort.

CHAIRMAN MCDERMOTT: Therefore, they are not established.

DR. CLUFF: Although Dr. Eichenwald has shown that infants with viral respiratory infection may disseminate more readily into the air staphylococci colonizing in the nose, I do not believe we have thoroughly defined why certain individuals are air disseminators, whereas others are not. It is possible that environmental conditions of humidity, structural characteristics of the respiratory tract, and many other factors may be important determinants of the capability of an individual to spread his organisms by the airborne route.

CHAIRMAN MCDERMOTT: I think the concept of the dangerous disseminator, which Dr. Langmuir has done so much to present, is very important. I would like to know whether we have the techniques to study this problem. Dr. Eichenwald has shown some of the variations in staphylococcal disease and Dr. Riley has studied tuberculous disease. Can anybody, from the standpoints of physics and aerodynamics, answer whether we are well equipped to study these disseminators now? That is, is there any need for wind tunnels or mud floor huts or anything like that, or can we study disseminators with the equipment we now have?

DR. LANGMUIR: It is difficult to study them. Consider the air sampler that Dr. Riley has to build for 150 guinea pigs in a chamber; it is an expensive system and the duration of experiments must be 1 month or more. This is about as difficult a sampling process as I know. I argue that of course the full details are not established, but the idea, the working concept, is formulated. Starting with the infected family, what is the character of the new case that has broken down and promptly infected the family compared with the many that do not? What is the character of the individual in each epidemic situation? Answers to such questions would give us many important leads, it seems to me, for further work, which may require the use of a device as elaborate as Dr. Riley's.

PROF. HATCH: I wonder if these questions were raised 50 years ago, about typhoid fever, for example. Or, were the major avenues of spread of the disease demonstrated by showing the effectiveness of certain control measures, such as cleaning up the water supply and pasteurizing the milk?

CHAIRMAN MCDERMOTT: There is a partial answer, Professor Hatch. It all depends on the circumstances; for instance, how tuberculosis was spread was a matter of really complete unimportance when everybody had tuberculosis and when there was not a great deal that you could do about it. But, now, when in this part of the world relatively few people have the disease, it becomes important to find out how it spreads. In the vast areas of the world where we are treating people and drug-resistant strains appear in mud floor huts, suddenly great importance is attached to finding out exactly how the agents are transmitted.

PROF. HATCH: Certainly, the need for sharp

differentiation increases as the magnitude of the problem decreases, but I still think we are not giving enough attention to the question of preventive procedures. The best way to show the importance of aerial spread of disease is to show that the spread can be prevented by effective disinfection of the atmosphere breathed in common by infected and susceptible individuals.

DR. FRANCIS: I do not think John Snow (12) fully answered this particular question. I would like to point out, however, that as the amount of pulmonary tuberculosis declines, opportunities to see these sharply defined instances should thereby improve. We should then be able to bring in the battery of considerations raised here and test them, whether it is the strain, or this or that. At least we could pick out the episodes in much clearer fashion than if we were in the middle of a period of terrifically high constant activity.

DR. MIDDLEBROOK: For the purpose of stimulating panel discussion, I suggest that during this Conference there has arisen only one decisive question with regard to the importance of the air as a bearer of agents of infectious diseases, a well-defined question which we have not really attempted to answer. Perhaps there is a way of expressing the question which will help to clarify the public health issues involved as well as to define a little more precisely what experimental approaches might be most promising. First, it is well known that only small particles stay in the air long enough to be affected by either of two devices, either ventilation or disinfection of various kinds, especially radiation. This is a physical fact.

Now, at the point where one says, "That particle is too big," he is beginning to quibble. We have at all points recognized that this is a statistical problem, and we beg the issue by getting worried about whether we are cutting off at the right level. Here again, I point out that it depends on how hard the wind is blowing. As Dr. Perkins pointed out, rather large particles might be able to stay up quite a while if there is a lot of eddying.

Second is the basic biological aspect. How important epidemiologically are these small particles as bearers of infection under most natural conditions; I emphasize, conditions as they occur in practice?

The reason I think it is important epidemiologically to state the question so precisely is that then we can do something in practice, like controlling our water supply. We already do some things, but perhaps from a technical, analytical standpoint the measures are not good enough about ventilation and about sterilization of the living particles or agents that are in these particles in the air.

It seems to me that this is the area where disagreement has been occurring. Basically, the question is, just what do small particles do? The large ones we cannot do much about, but what about the small ones? What is their biological importance? Because we can perhaps do something about them through irradiation and ventilation engineering, I wonder if stating the question this way might make it more fruitful for the panel to consider.

CHAIRMAN MCDERMOTT: In effect, you made a very elegant plea for selecting those groups of infections which have in common the fact that they can spread more than 6 ft from host to host, through the air, and in some cases for very long periods. Indeed, that has been the focus of this Conference, and as with any other conference nobody can tell quite how it will come out before it is held. It seems to me that our gathering together here and considering diseases from this single common point of view has been very well justified by the proceedings of the past 2½ days. We have heard a wealth of information, much of it beautifully quantitative and some of it pointing out the great gaps in our knowledge of this area.

I judge that Dr. Langmuir discussed control in his presentation about as much as he wishes. If I am wrong, Dr. Langmuir, and there are other things you wish to say about control, go right ahead.

DR. LANGMUIR: I think control measures applied to specialized situations, as in laboratories, have been developed to a magnificently precise degree. But to control all the air that we breathe in our daily associations is an utterly different engineering function than controlling the water supply or pasteurizing the milk.

DR. DAVENPORT: I think the question concerning equipment was raised before, and Dr. Francis made the comment about emphasis on the study of the kinds of particles that emanate. I return and ask the question again. Is there a consensus that equipment to characterize the

emanations from sick patients with various respiratory diseases is adequate, or are we confusing the issue; that is, do we have good equipment to make an infecting atmosphere but not good equipment to study an already infected one?

DR. GLASSMAN: My earlier remarks referred to equipment for experimentally generating microbial aerosols and subsequent sampling by exposure of appropriate hosts and mechanical sampling devices. The quantities of microorganisms emanating from individual patients ill with respiratory disease may in some instances be so small that difficulties are encountered in applying currently available air-sampling techniques.

CHAIRMAN MCDERMOTT: The most impressive feature of this Conference, perhaps, was the great increase in understanding between the people with considerable knowledge of physics and aerodynamics and the people with the more purely microbiological approach. Also, several important areas for future exploitation have been outlined.

If we were to bring together a contemporary Frenchman and a contemporary American and ask them to talk to each other, they would not talk in Parisian French or Oxford English, but rather in atrocious French and broken English. If to a considerable extent our discussions during the past days have to some of us been atrocious French and broken English, at least information is starting to get across. The time may come when this group, or groups similarly concerned with these problems, may be able to talk with the most beautiful Oxford accents, which everybody then will understand.

Now I would like to thank the chairmen and call on Dr. Cannan.

DR. CANNAN: Thank you, Mr. Chairman, for this opportunity to express the indebtedness of the Division of Medical Sciences of the Academy-Research Council to all participants in this Conference. Our thanks are due particularly to you, sir, for your able and debonair leadership, and to the chairmen of the several sessions. You have all contributed much on the scene and behind the scenes to assure that the proceedings would advance smoothly, logically, and with grace. You have all accepted the challenge of the problem and have invested it with zest and vitality. This was our hope and purpose.

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